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# **Computerised exposure therapy for Spider Phobia: Effects of cardiac timing and interoceptive ability on subjective and behavioural outcomes**

Running Title: Interoceptive effects in spider phobia treatment.

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## **CONFLICT OF INTEREST**

The authors named on this paper have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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## **Abbreviations**

SPQ – Spider Phobia Questionnaire

BAT – Behavioural Avoidance Task

DPSSr - Disgust Propensity and Sensitivity Scale Revised

ECG - Electrocardiography

SCR – Skin Conductance Response

$\eta_p^2$  - Partial eta-squared

## ABSTRACT

**Objective:** Spider phobia is a common form of anxiety disorder for which exposure therapy is an effective first-line treatment. Motivated by the observed modulation of threat processing by afferent cardiac signals; we tested the hypothesis that interoceptive information concerning cardiovascular arousal can influence the outcomes of computerised exposure therapy for spider phobia.

**Method:** Fifty-three normal healthy participants with high spider phobia scores underwent one of three modified computerised exposure protocols, defined by the timing of exposure to brief spider stimuli within the cardiac cycle: Systole (during afferent baroreceptor firing); Diastole (during baroreceptor-quiescent interbeat interval); Random (non-contingent on cardiac cycle). Outcomes were judged on phobic and anxiety measures and physiological data (skin conductance). Subjects were also rated on interoceptive accuracy.

**Results:** Mancova analysis showed that timing group affected the outcome measures ( $F(10,80)=2.405$ ,  $p=0.015$ ) and there was a group interaction with interoception ability ( $F(15,110)=1.808$ ,  $p=0.045$ ). Subjective symptom reduction (SPQ) was greatest in the Systolic group relative to the other two groups (Diastolic ( $t=3.115$ ,  $p_{\text{tukey}}=0.009$ ); Random ( $t=2.438$ ,  $p_{\text{tukey}}=0.048$ ), with greatest reductions in those participants with lower interoceptive accuracy. Behavioural aversion (BAT) reduced more in cardiac-contingent groups than the non-contingent (Random) group (Diastolic ( $t=3.295$ ,  $p_{\text{tukey}}=0.005$ ); Systolic ( $t=2.602$ ,  $p_{\text{tukey}}=0.032$ ). Physiological (SCR) responses remained strongest for spider stimuli presented at cardiac systole.

**Conclusion:** Interoceptive information influences exposure benefit. The reduction in the subjective expression of fear/phobia is facilitated by 'bottom-up' afferent signals; while improvement in the behavioural expression is further dependent on 'top-down' representation of

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self-related physiology (heart rhythm). Individual interoceptive differences moderate these effects, suggesting means to personalise therapy.

Key Words: Exposure Therapy, Phobia, Interoception, Cardiac Timing

## INTRODUCTION

Spider phobia is a specific phobia and recognised mental disorder, in which affected individuals display an enduring fear of, and rapid physiological and psychological reaction to, specific objects or situations; in this case, spiders. This reaction is typically perceived as beyond volitional control, disproportionate and irrational.

Specific phobias are common and chronic, with lifetime prevalence of around 8% (1,2). There is high co-morbidity with other disorders, including depression (2). Phobic individuals can be reluctant to seek help and often refuse treatment so there is a large undiagnosed and untreated population (3). Specific phobias typically lead to restricted, reduced quality of life (4).

A hyper-reactive threat detection system is implicated in specific phobia (5). Within the brain, hyper-reactivity to the threat stimulus is reported, resembling activation patterns evoked by learnt and conditioned threats (6,7). Fear conditioning can be promoted by heightened sensitivity to internal bodily arousal and 'phobic avoidance' may be adopted to manage the psychological impact of physiological arousal (8). Thus, phobic behaviours may reflect individual sensitivity to internal body signals (interoception) and a misinterpretation of the level of threat they imply.

Exposure therapy is the first line treatment for specific phobia (6,9). In exposure therapy the core principal is to expose individuals systematically and repeatedly to feared and avoided stimuli within a controlled environment. By successfully confronting phobic stimuli, the fear response is modified, creating a new 'safe' memory that diminishes feelings of distress and powerlessness. Fear extinction is critical to this process, whereby new associations suppress previously established fear responses. Fear extinction through effective exposure therapy attenuates neural hyper-reactivity within fear circuitry (6).

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Interoception describes the sensing of changes in the internal physiological state (10).

Interoception contributes to emotional feelings, such that individuals who are more able to accurately detect bodily signals (e.g. heartbeats) report more intense emotional experiences (11,12) and can be vulnerable to anxiety symptoms (13,14). Interoceptive information concerning physiological arousal influences the expression of anxiety in phobia (15,16). Within the brain, anterior cingulate and insular cortices, alongside the amygdala, influence how subjective experience is mediated by visceral information and emotional feelings (17), including threat (10,11,18). Interoceptive signals also influence memory processes. Heightened physiological arousal can enhance memory encoding (19), yet in other circumstances, it may interfere with memory (20,21) and decision making (22).

A key channel for afferent interoceptive signalling of cardiovascular arousal is the information from arterial (aortic and carotid) baroreceptor firing. These baroreceptors are pressure and stretch sensors that fire in bursts each time blood pumps from the heart at ventricular systole, and are quiescent between heartbeats, during diastole. The signals are conveyed by vagus and glossopharyngeal afferents to the nucleus of the solitary tract (NTS) and encode the timing and strength of individual heartbeats. This information is critical for control of blood pressure (via the baroreflex) and also impacts on perceptual and cognitive processing (23–25). The influence of this channel of cardiovascular interoceptive information on psychological (perceptual and cognitive) processes can be isolated by measuring responses to brief stimuli presented at systole, compared to at diastole. This approach controls for other confounding features of sustained states of physiological arousal. Cardiac afferent signals at systole typically inhibit stimulus processing, e.g. for pain (26,27), startle reflexes (28) and word encoding (29). However, these same cardiac afferent signals enhance the detection and processing of fear and threat stimuli (14,30). The impact of these cardiac afferent signals is also influenced by individual differences in interoceptive ability; for example people who perform more accurately

on heartbeat detection tasks are less susceptible to the inhibition of memory encoding by phasic baroreceptor signals (29).

In the present study, we tested the principle that cardiac interoceptive signals will modify outcomes of a computerised exposure therapy for spider phobia and thus offer a pathway to increased treatment efficacy. Our rationale was to base the experiment on the premise that controlled exposure to an aversive stimuli can reduce phobic response (31). Thus, we were interested in whether our cardiac manipulation had a further added benefit to classic exposure manipulations. To this end, we incorporated both a systolic and diastolic group, and a (smaller) control group (to control for the effects of mere exposure) to see whether cardiac timing might influence classic exposure effects. This by no means represents a comprehensive exposure therapy procedure but attempts to emulate one of its key components, the exposure to the phobic threat in a safe non-threatening environment. Participants were allocated to groups defined by the contingency of exposure stimuli to the phase of the cardiac cycle (Systole, Diastole and Random). Subjective, behavioural and physiological indices of phobic response were tested for effects of intervention and their interaction with heart timing. We also tested for the hypothesised influence of individual differences in interoceptive ability on therapy outcomes.

## **MATERIALS AND METHODS**

### **Participants**

Participants were recruited through advertisements posted on community websites and around the university campus. Volunteers completed an on-line version of the Spider Phobia Questionnaire (SPQ) (32). The SPQ is a 31 item self-report instrument that measures fear of spiders. Scores can range from 0 to 31 with higher scores indicating greater aversion. Those scoring 20 or above on the scale were invited to enrol. This cut-off is consistent with scores reported in other non-clinical studies of individuals considered to have high levels of phobia



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(mean (+/-sd)) (Hellstrom and Ost, 1995 – 20.7 (+/-2.6) (33); Muris and Merckelbach, 1996 – 23.2 (+/-3.0) (34); Teachman and Woody, 2003 – 19.7 (+/-4.8) (35); Li and Graham, 2016 – 21.0 (+/-3.0) (36). .

Recruitment and testing took place September 2014 and December 2015 with group allocation attempting to balance group SPQ scores, age and gender as the study progressed. A power analysis conducted on data from a smaller pilot study (unpublished) was used to estimate required group size (approx. 20-30 participants in each study arm). However, as the study proceeded, it became clear from recruitment patterns that this was unlikely to be met in the time available. Therefore, in the later phase, allocation to the cardiac timing groups was prioritised. In addition, in contrast to the pilot, four exposures (instead of two) were used to amplify any cardiac effects.

Nearly 270 individuals completed the questionnaire of which 58 individuals were recruited and assigned to one of three distinct timing groups: 22 participants to a Systolic group, (i.e. spider image presentation at systole, simultaneous with afferent baroreceptor signalling); 22 participants to a Diastolic group (spider images presented at diastole); and 14 participants to a Random (Control) group (images presented randomly over the cardiac cycle

Participants provided written informed consent for the study approved by Brighton and Sussex Medical School Research Governance and Ethics Committee. Participants were recruited in the knowledge that this was a research study conducted for proof of concept reasons (and in full accordance with ethical approvals) and not a formal clinical intervention, managing expectations.

Because of data loss, 54 of the 58 participants ultimately entered data analyses. (21 Systolic, 21 Diastolic and 12 in Random group).

## **Procedure**

At the first attendance, each participant completed self-report questionnaires, and underwent assessment of their interoceptive abilities. Assessments included collection of key demographics, SPQ, Anxiety state and trait questionnaires (37), Disgust Propensity and Sensitivity Scale Revised (DPSSr) (38) and a behavioural avoidance task (BAT). Participants were scheduled for four exposure sessions, separated by a minimum of 2 days. Assessments were repeated after completion of the last exposure session.

### **Behavioural Avoidance Task (BAT)**

The BAT is an objective behavioural measure of phobia (39). Participants entered the testing room. At the opposite end, a spider moult (large Mexican red knee tarantula) rested in a clear plastic container. Progress was scored according to 7 stages of approach: from outside (stage 0), 5m from container, 3m from container, at the container, opening the lid, placing hand inside for a few seconds, touching the spider with a pencil tip for a few seconds, and lastly touching the spider with a finger for a few seconds. At each achieved stage, participants gauged their anxiety on a scale 0 to 100. The final 'approach' score was the 'stage' number reached (max 7). Participants could escape the task at any point and were timed-out (after 15 secs) following hesitation to progress further.

### **Exposure therapy sessions**

Participants first completed the Anxiety state questionnaire before viewing 4 blocks of spider images. Each block contained 40 images, 35 depicting spiders and 5 abstract shapes. Images were drawn from a stock of 220 spider images, representing a random selection of world spiders. Each block contained a different sequence of images. For the four exposure sessions, block content was counterbalanced so that each participant saw the same images the same number of times over their sessions.

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Participants sat one metre in front of a 15-inch display monitor (Cathode Ray Tube CRT). Each image was presented for 100 msec. Between presentations, a black fixation cross was visible in the centre of a white background. In each block, six of the images were followed by a computerised visual analogue scale (VAS), which the participants used to rate their subjective impression of that image's 'intensity' (this data is not included here). To further encourage attentional engagement, a small number of the spider images in each block showed a black disc superimposed on the spider's abdomen. During viewing, participants made a keypress every time they noticed such an image.

Each block lasted approximately 5 minutes and was followed by a one-minute rest period. A Likert self-report VAS was used to report current anxiety level between the exposure blocks and before and after sessions. The participant marked their anxiety level on a line marked zero to 100 percent.

### **Detection of heartbeats**

Cardiac timing was determined using electrocardiography (ECG). ECG waveforms were conditioned (CED 1902 amplifier), digitized (CED Power 1401) and stored on a PC (Spike2 v7 software; CED). Stimulus timing was controlled by a script running in Spike2, identifying the QRS complex. For the heart timing groups (Systolic and Diastolic), image presentation was either time-locked to 300 msec from the R-wave peak to coincide with the peak period of ventricular systole (when baroreceptors are activated and their impulses are processed centrally) or to the R-wave itself (end of cardiac diastole) (23,25). For the third control (Random) group, the presentation was not time-locked to cardiac signals.

### **Electrodermal activity**

Skin conductance responses (SCRs) were recorded to index evoked changes in centrally-driven electrodermal activity mediated by fluctuations in sympathetic activity associated with emotional

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arousal and attention via the sudomotor nerves (40). Electrodermal activity was recorded with a CED 2502 skin conductance unit (CED) using 8 mm Ag/AgCl cup electrodes with isotonic electrode paste affixed to the middle phalange of second and third fingers of the left hand. As SCRs are typically delayed by at least a second following stimulus, SCRs were scored as changes in conductance (micro Siemens) starting in the 1–4-s interval after onset of each stimulus. Three measures were used: The average number of SCRs detected, defined as change of  $>0.01 \mu\text{S}$  from baseline; the average SCR amplitude within the response window after thresholding ( $>0.01 \mu\text{S}$ ) and the average amplitude of SCRs within the response window without thresholding. All analyses were performed with Ledalab (41).

## Interoceptive ability

Individual differences in interoceptive accuracy was indexed from performance of heartbeat detection tasks, using heartbeat counting (42) and heartbeat discrimination task (43). Both tasks have recognised psychometric limitations (44); though retain inferential validity as measures of individual differences in interoceptive performance (45). Focus is given here to findings from the heartbeat counting task, which is more suited to application to regression analyses, separating individual performance along a normative distribution.

In the heartbeat counting task, participants counted felt heartbeats over different time intervals. The average ratio score, i.e. ratio between the reported number and the real number of heartbeats was calculated across six trials (46).

## Data Analysis

One subject was lost to the analysis procedures because of corrupted interoception data. Another was lost to the analysis of the physiological data because they failed to produce any detectable SCR response during testing. Statistical analyses of self-report and behavioural measures were conducted using SPSS22. Repeated measures analysis of covariance was

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used to establish intervention effects on phobic levels and anxiety scores. A multivariate (general linear model) analysis of variance was then run to determine effects of group membership on the key dependent variables (Final SPQ, BAT, Disgust and Trait Anxiety scores) as these each reflect different elements of the overall phobic experience. Baseline values were included as covariates along with interoception accuracy. Follow-up analysis of covariance was used to explore significant main effects and interactions. Simple regression models were then used to understand the origin of any interactions detected and regions of difference.

Statistical analyses of physiological variables included three electrodermal skin conductance response (SCR) measures (Number of detected SCRs to spider images, average SCR phasic amplitude (thresholded) and average SCR phasic amplitude (unthresholded)). These key physiological measures were entered an identical analysis process to the one outlined above.

## RESULTS

### Impact of exposure intervention on subjective and behavioural symptoms of spider phobia

Table 1 presents summary demographic and key behavioural data for the three cardiac timing groups before and after treatment. Pair-wise tests showed no marked differences between groups for any of the baseline measures. Of the subjects tested 41 participants (76%) showed improvement on SPQ while 7 showed no change and 6 slight decrements (1 or 2 questions). For BAT, 37 (69%) showed improvement, 15 were unchanged and 2 displayed a small decrement (one stage).

Overall subjective symptoms decreased after the exposure sessions (SPQ,  $F(1,53)=37.540$ ,  $p<0.001$ ,  $\eta_p^2=0.415$ ). Behavioural expression of aversion also decreased (BAT,  $F(1,53)=41.732$ ,  $p<0.001$ ,  $\eta_p^2=0.440$ ). Disgust rating ( $F(1,53)=5.710$ ,  $p=0.020$ ,  $\eta_p^2=0.097$ ) and State anxiety

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( $F(1,53)=24.86$ ,  $p<0.001$ ,  $\eta_p^2=0.319$ ) also reduced. Exposure therapy did not change Trait anxiety ( $F(1,53)=1.898$ ,  $p=0.18$ ,  $\eta_p^2=0.035$ ). No correlation was found between State ( $r^2=0.018$ ,  $p=0.33$ ) or Trait anxiety ( $r^2=0.008$ ,  $p=0.510$ ) and interoceptive accuracy, suggesting no overall relationship between anxiety level and interception ability in these phobic subjects.

The consistency of timing of image presentation with cardiac cycle was checked across the three timing groups. As expected and previously reported from this lab (see Fig. 1, Garfinkel, Minati, et al., 2014)(47), for systolic and diastolic presentation, stimuli clustered around the ventricular systole and quiescent diastole phases respectively. In the random group, image timing was uniformly distributed across the beat interval.

A repeated-measures analysis of variance on the Likert anxiety data showed that anxiety levels dropped across the blocks within each exposure session ( $F(4,204)=14.186$ ,  $p<0.001$ ,  $\eta_p^2=0.218$ ), and there was a block by exposure interaction ( $F(12,612)=41.534$ ,  $p<0.001$ ,  $\eta_p^2=0.449$ ) signifying that anxiety dropped more rapidly over blocks as sessions progressed. There were no group differences.

The multivariate analysis indicated that group membership had an important influence on the outcome measures (Final SPQ, BAT, DPSS and Anxiety trait scores) (Wilk's  $\lambda=0.594$ ,  $F(10,80)=2.405$ ,  $p=0.015$ ) and showed a group by interoception interaction (Wilk's  $\lambda=0.546$ ,  $F(15,110)=1.808$ ,  $p=0.045$ ). Thus cardiac timing was influencing phobic phenomena and interoception ability was modulating this effect.

Between-subjects results showed a significant group effect and group by interoception interaction for Final SPQ and BAT scores (detailed in post-hoc analysis below) but not for Disgust or Anxiety trait. Both initial SPQ and BAT scores were found to be specific predictors of final SPQ and BAT scores respectively (Initial SPQ,  $F(1,43)=34.015$ ,  $p<0.001$ ; Initial BAT,

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$F(1,43)=28.405$ ,  $p<0.001$ ) and are included in relevant post-hoc models. Neither initial Anxiety trait score nor Disgust score showed any influence on the final SPQ or BAT values.

## Cardiac influences of exposure intervention on subjective spider phobia symptoms

Follow-up analysis of covariance for SPQ (modelling group, interoception accuracy and group by interoception interaction (initial SPQ as covariate) confirmed a group main effect ( $F(2,46)=5.515$ ,  $p<0.007$ ,  $\eta_p^2=0.193$ ). The Systolic group had significantly lower scores relative to the other two groups (SPQ\_Final; Diastolic ( $t=3.115$ ,  $p_{\text{tukey}}=0.009$ ); Random ( $t=2.438$ ,  $p_{\text{tukey}}=0.048$ ), suggesting a greater efficacy of the exposure treatment at cardiac systole. There was a significant group by interoception accuracy interaction ( $F(2,46)=6.176$ ,  $p=0.004$ ,  $\eta_p^2=0.212$ ). Beneficial effects of cardiac timing on phobic reduction at systole were mediated by an individual's interoceptive ability. No interoception accuracy main effect was found. Parameter estimates of the regression slopes of final SPQ against interoceptive accuracy show that accuracy influenced score in the Systolic group ( $B=25.799$ ,  $t(20)=3.754$ ,  $p=0.001$ ; see Table 2). The observed improvement in verbal-cognitive phobia scores observed for individuals exposed to spiders at systole (i.e. during afferent baroreceptor signalling) was driven by effects in individuals who were least accurate in heartbeat detection task performance.

To explore regions of significance, participants were divided according to heartbeat detection accuracy into 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentiles (corresponding to accuracy levels of 0.53, 0.65 and 0.79; representing poor, moderate and good interoceptive ability (Fig. 2). Group and group by interoceptive accuracy interaction were entered as variables of interest in the models. When interoceptive accuracy performance was poor, there was a greater reduction in subjective symptoms with Systole, compared to Diastole ( $F(1,47)=5.733$ ,  $p=0.020$ ) or Random ( $F(1,47)=12.524$ ,  $p=0.001$ ) cardiac timing. The positive advantage for Systole compared to Random presentation was retained at the 50<sup>th</sup> percentile ( $F(1,47)=4.792$ ,  $p=0.030$ ).

***Summary of cardiac timing effects on subjective response to computerised exposure intervention***

Subjective aversion to spiders showed most improvement in self-reported spider phobia symptoms if exposure intervention occurred at cardiac systole, i.e. synchronous with afferent baroreceptor signalling of cardiovascular arousal. Individuals with poorer interoception showed the greatest subjective benefit from linking spider exposure to cardiac afferent signals. This advantage was absent for those with better ability.

**Cardiac influences on objective behavioural aversion to spiders following exposure intervention.**

Across all participants, subjective (BAT) scores correlated inversely with SPQ ( $r^2=-0.175$ ,  $p=0.002$ ), indicating that subjective and behavioural measures of phobia share some association but perhaps measure different dimensions of the phobic response.

Analysis of covariance (modelling group, interoception accuracy and group by interoception (initial BAT as covariate) confirmed group as a main effect ( $F(2,46)=5.691$ ,  $p=0.006$ ,  $\eta_p^2=0.198$ ) and group by interoception interaction ( $F(2,47)=5.160$ ,  $p=0.010$ ,  $\eta_p^2=0.183$ ). The Random group had significantly poorer improvement relative to the other two groups (BAT\_Final; Diastolic ( $t=3.295$ ,  $p_{\text{tukey}}=0.005$ ); Systolic ( $t=2.602$ ,  $p_{\text{tukey}}=0.032$ ), suggesting a greater efficacy of the exposure therapy with cardiac synchronisation. Possibly 'self-context', evoked by predictable relationships with heartbeat, facilitates successful behavioural extinction of phobic fear compared to 'non-cardiac contingent' exposure to the same stimuli. The interaction signifies a difference between groups as a function of interoceptive accuracy. Parameter estimates of the regression slopes of final BAT against interoceptive accuracy (Table 2) indicate that the Random group displayed more improvement if they were better able to perceive their heartbeats



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accurately (positive co-efficient) ( $B=5.504$ ,  $t=2.148$ ,  $p=0.057$ ) whilst both Diastolic and Systolic groups did not.

The extent of this mitigating effect of interoception accuracy in the Random condition is illustrated in Figure 3 where participants are divided by their ability. At the 25<sup>th</sup> percentile both Diastolic ( $F(1,47)=8.121$ ,  $p=0.006$ ) and Systolic ( $F(1,47)=7.844$ ,  $p=0.007$ ) produced better exposure results than Random presentation. This pattern was repeated at the 50<sup>th</sup> percentile (Diastolic,  $F(1,47)=5.367$ ,  $p=0.025$ ; Systolic,  $F(1,47)=4.737$ ,  $p=0.035$ ).

### ***Summary of cardiac timing effects on behavioural response to exposure intervention***

The exposure protocol reduced behavioural avoidance, particularly if presentation was contingent upon an individual's heartbeat (diastole or systole). This suggests that 'self-context' (linking phasic somatic signals to external (aversive) events) enables a more effective extinction of fear behaviour. Moreover, when bodily context was not explicitly coupled to image presentation, individuals with better interoceptive ability manifest behavioural improvements equivalent to the other (heart timing) groups.

### **Impact of exposure intervention on physiological indices of spider phobia**

Over the course of exposure treatment, phasic electrodermal responses (SCR: evoked changes in electrodermal activity mediated by sympathetic sudomotor nerves) reduced in number and amplitude (repeated measures ANOVAs: detected SCR,  $F(3,150)=7.01$ ,  $p<0.001$ ,  $\eta_p^2=0.126$ ); average thresholded SCR amplitude,  $F(3,150)=5.445$ ,  $p=0.001$ ,  $\eta_p^2=0.101$ ) and unthresholded SCR amplitude,  $F(3,150)=5.74$ ,  $p=0.001$ ,  $\eta_p^2=0.101$ ). No measure showed a group-by-time interaction.

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The multivariate analysis failed to find a group effect or a group by interoceptive accuracy interaction. Initial SPQ, Disgust and BAT scores, nor Trait Anxiety level were predictors for any of the physiological indices at end of therapy.

Post-hoc Ancova analyses, modelling only group and group by interoception accuracy demonstrated a significant group by interoception accuracy interaction for number of SCRs detected ( $F(3,47)=5.950$ ,  $p=0.002$ ,  $\eta_p^2=0.154$ ), and average thresholded ( $F(3,47)=4.519$ ,  $p=0.007$ ,  $\eta_p^2=0.155$ ) and unthresholded SCR amplitude ( $F(3,47)=4.071$ ,  $p=0.010$ ,  $\eta_p^2=0.113$ ). Thus, interoceptive accuracy may augment cardiac afferent effects on physiological reactions. Parameter estimates of the regression slopes for these physiological measures (see Table 2) indicate that the Systole group retained larger physiological reactivity by end of therapy if they possessed better interoceptive ability (illustrated in Fig. 4 for SCR amplitude). 'Good interceptors' (75<sup>th</sup> percentile) showing significantly greater electrodermal responses to stimuli, with more detected events ( $F(1,45)=10.354$ ,  $p=0.002$ ) and higher average thresholded ( $F(1,45)=11.339$ ,  $p=0.002$ ) and unthresholded ( $F(1,45)=12.064$ ,  $p=0.001$ ) SCR amplitude in the Systole than Diastole presentation.

### ***Summary of cardiac timing effects on physiological response to computerised exposure therapy***

There was a general reduction in electrodermal reactivity to spider stimuli, consistent with improvement in the physiological expression of fear response. However, the data suggests that electrodermal activity is a weaker measure of cardiac timing influences on therapeutic response than subjective or behavioural indices. Nonetheless, SCR responsivity was enhanced by systolic timing and correlated, across the whole group, with interoceptive accuracy ( $r^2=0.142$ ,  $p=0.002$ ).

## DISCUSSION

The study was predicated on previously observed effects of heartbeat timing on processing of threat, in which the detection and perceived intensity of fear signals is enhanced by cardiac systole, during arterial baroreceptor firing (48). Moreover, effects of heart timing on stimulus processing can be moderated by interoceptive ability, as measured by heartbeat detection tasks. People who are 'good heartbeat detectors' may demonstrate a reduced impact of afferent systolic signals on stimulus processing (49). As such it represents proof of principle work based on the integration of cardiac timing and interoceptive signals toward refinements in exposure therapy approaches.

Overall the methodology reduced subjective, behavioural and physiological measures of phobic response. However, a proportion of participants showed little improvement in phobic response. This is consistent with clinical implementations of exposure therapy models, (31). Embedded within these outcomes were interactions between effects of heart timing and individual differences in interoceptive accuracy.

The subjective sense of threat from spiders indexed by the SPQ showed greatest decrease overall when exposure occurred at systole. This finding suggests better perceptual processing of putative threat stimuli (50), hence greater 'psychological exposure' to facilitate extinction learning. Theoretically, the enhancement of perceptual processing by afferent baroreceptor signalling may be mediated by cardiac-gated noradrenaline release from locus coeruleus (51,52). The systolic influence on subjective threat extinction was also dependent on another aspect of cardiac interoception, heartbeat detection accuracy. Here, better interoceptive accuracy suppressed the impact of afferent systolic signals on subjective extinction of phobia. Interestingly, electrodermal activity, a physiological expression of threat (SCR evoked changes in electrodermal activity mediated by sympathetic sudomotor nerves), also mirrored this

interaction, i.e. people with better interoceptive accuracy showed greater retention of the physiological fear response at the end of the therapy. This suggests a connection; perhaps through descending 'predictive' influences of enhanced interoceptive ability on midbrain monoamine nuclei, influencing both perceptual precision and efferent sympathetic outflow (53).

Baroreceptor firing represents a key mechanism for central communication of physiological arousal (heart rate and blood pressure increases). Thus, one implication of our findings is that people might extinguish subjective threat of spiders if learning occurs during states of heightened physiological arousal. This can seem counterintuitive, as the experience of arousal engendered by seeing a spider might associatively reinforce the psychological representation of threat. However, potentially this effect might be specific to the exposure task, where the brief presentation of spiders is synchronous with a systolic arousal signal that provides a context, rather than a consequence, and which then predicts the ensuing diastolic (quiescent) phase.

The expression of fear memories may be altered by two related mechanisms. First, extinction through repeated non-reinforced re-exposure to a conditioned stimulus. This engenders the formation of a new competing 'safe' memory. The fear response to the conditioned stimulus is subsequently attenuated (54). Secondly, reconsolidation occurs when a previously acquired memory becomes labile when retrieved (e.g. during re-exposure) and requires restabilizing (55,56). Reconsolidation can strengthen fear memories (57) but also provides a mechanism to reconfigure and reduce such memories (55,58,59). Extinction is often considered a form of learning (54,60,61), yet reconsolidation is a property of retrieval (61,62). These two processes can occur independently, possibly both via the amygdala (57,60,63).

While the influence of systolic signals on threat processing is facilitatory (e.g. enhancing fear detection and perceived intensity (47,48)), cardiac signals can be distracting or inhibitory, typically interfering with perceptual processing (64). For example, there is suppressed

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processing of pain (48,65). The encoding of words is also inhibited at systole, yet better interoceptive ability (heartbeat detection accuracy) diminishes this deleterious effect (29). This observation parallels our observation that enhanced interoceptive accuracy countered the (enhancing) effect of systolic signals on extinction memory.

Effective exposure therapy aims to improve both the subjective and behavioural expression of spider phobia. Nevertheless, fear behaviour arguably represents the most pragmatic way to index phobia and quantify the effectiveness of exposure interventions. Individuals who underwent exposure to spiders presented contingent with their own heartbeat (i.e. either at systole or at diastole) showed better behavioural extinction of phobia (i.e. could approach closer to a spider moul) than those whose exposure was non-contingent on their heartbeats. The implications here are 1) that the effect on behavioural extinction of phobia is driven by a different mechanism to the systole-enhanced extinction of subjective phobia, 2) this mechanism depends more on a predictable relationship between cardiac physiology and external stimulus, than on the afferent baroreceptor input from individual heartbeats. This effect may represent the suppressed processing of self-relevant stimuli (66,67), in this instance diminishing the sense of threat to facilitate new safety learning. Since the behavioural effect is not dependent on the exact phase of the cardiac cycle, it is likely mediated by a higher-order predictive representation of the rhythm of cardiac signals, rather than phasic afferent baroreceptor firing. The same process may account for why good interoceptive accuracy (measured using heartbeat detection task) reduced behavioural avoidance after exposure therapy in the Random group. In the somatomotor system, the brain anticipates the sensory consequences of one's own actions through corollary discharge. This typically results in attenuated sensory processing, but also helps distinguish self-generated from externally generated stimuli (68,69). Such effects are also observed for external stimuli controlled by the self (70–72). Theoretically, interoceptive bodily signals, and their predictive representation, underpin neurobiological representation of self

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through a sense of internal agency (67,73). However, there is little empirical research exploring the link between agency and interoception. The suppressed processing of exteroceptive information when synchronised with interoceptive cardiac signals is reported in an electroencephalography study. Independently of timing delay, evoked potentials (N1 ERP component) to auditory stimuli synchronized with heartbeat signals are suppressed when compared to asynchronous stimuli (74). This effect was attributed to top-down modulation of sensory inputs by visceral representations, probably in insular cortex (10,17). Our own findings suggest a similar mechanism may be valuable therapeutically: The integration of cardiac timing with presentation of the phobic stimuli may reduce mismatch between expected and observed interoceptive signal, thereby inhibiting avoidant behaviours. It is believed that this mismatch is critical for the new learning and development of inhibitory expectations that will compete with threat expectancies (9). Such enhanced precision of interoceptive predictive models on which to base new learning, putatively reduces anxiety and improves subjective sense of control (8,75). The link to interoceptive accuracy is also informative when considering how to tailor the therapeutic intervention to individuals.

In summary, we highlight the effects of cardiac timing and the modulatory influence of interoceptive ability on response to the exposure protocol. We also note dissociation between subjective and behavioural response systems in their relationship to bottom-up and top-down interoceptive representations. Subjective-behavioural dissociation is previously acknowledged in the expression of fear responses (76,77), yet might depend on questionnaire content (78): The SPQ does not index fear of harm (79), which may better predict behavioural avoidance (34). Nevertheless, our findings illustrate how aspects of interoception can facilitate the expression of subjective, behavioural and physiological therapeutic benefits of exposure therapy. For example; screening for those individuals with poor interoceptive ability and then exposing them to phobic items at systole could augment both subjective and behavioural responses to future

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interventions, leading to a more efficient and patient led treatment response. These insights can inform fresh treatment approaches, e.g. by refinement of our proof-of-principle integration of physiology with computerised exposure therapy, or by pharmacological targeting of central interoceptive pathways to augment conventional exposure approaches.

This report does suffer from several limitations. The study numbers are relatively small with an imbalance in numbers across groups due to prioritising allocation to the cardiac timing pools. Also, without a classical non-treatment control group, the extent to which we can quantify the magnitude of established exposure effects is constrained. However, our focus was on the specific impact of cardiac manipulation and to see whether this might provide mechanistic insight into factors that could enhance efficacy in future work. Group numbers within the study are modest and replication is required. Also, follow-up was unavoidably limited so whether differences persist longer term remains unknown.

In this study no assumption was made about how interoception signals were being interpreted by the participants. A positive relationship between accuracy in heartbeat detection and physiological variables such as anxiety and anxiety sensitivity has been noted (80). In anxiety disorders, increased self-report of somatic sensations and increased cardiac interoception sensitivity has been coupled to a subsequent dysfunctional cognitive appraisal of the sensations with a significant bias towards danger-related and catastrophizing interpretation of these cues. Prior work has demonstrated that individuals with high anxiety sensitivity and anxiety have a tendency to catastrophize body sensations (81,82). Attribution of positive or negative valence to sensed cardiac signals was not directly assessed here. Using experimental interoceptive challenge or validated questionnaire measures to explore dysfunctional cognitive appraisal of bodily sensations may be a useful extension in future studies.

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Finally, we constructed an exposure platform suited to laboratory constraints but detached from a comprehensive psychological treatment protocol. This may have contributed to the modest reductions we see in phobia levels. Typically programmes with exposure procedures are embedded in comprehensive Cognitive Behavioural Therapy environments and produce greater benefit. Effects of integrating heart timing into such treatments remains to be tested.



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## TABLES

Table 1 – Summary of key population, behavioural and interoception measures by group (mean and sd).

	<b><i>Random</i></b>	<b><i>Diastolic</i></b>	<b><i>Systolic</i></b>
<b><i>Population</i></b>			
N (M/F)	12 (1/11)	21 (4/17)	21 (3/18)
Age (years)	23.4 (8.71)	21.1 (4.96)	24.33 (8.99)
BMI (kg/m <sup>2</sup> )	22.6 (2.37)	22.0 (2.75)	24.7 (5.71)
<b><i>Behavioural</i></b>			
SPQ_Init	24.75 (2.63)	24.0 (3.13)	22.52 (3.28)
SPQ_Final	23.08 (2.39)	20.67 (4.08)	19.86 (6.04)
STAI_Y1_Init	45.33 (9.97)	42.14 (9.21)	36.95 (9.51)
STAI_Y1_Final	36.33 (8.87)	37.81 (8.40)	32.14 (7.88)
STAI_Y2_Init	43.08 (10.49)	46.86 (11.59)	41.48 (10.61)
STAI_Y2_Final	41.92 (10.26)	45.14 (10.31)	39.67 (7.72)
DPSSr_Init	50.25 (6.00)	49.57 (10.47)	46.14 (10.05)
DPSSr_Final	48.75 (8.81)	46.52 (11.48)	45.29 (8.33)
BAT_Init	3.07 (1.03)	3.81 (1.54)	4.43 (1.66)
BAT_Final	4.33 (1.72)	5.48 (1.89)	5.43 (1.66)
<b><i>Interoception</i></b>			
Tracking_Acc (%)	71 (18))	68 (16)	64 (15)

Key: SPQ – Spider Phobia Questionnaire; STAI\_Y1 – State Anxiety; STAI\_Y2 – Trait Anxiety; DPSSr – Disgust Questionnaire; BAT – Behavioural Avoidance Task; Tracking\_Acc – Interoception Tracking Task.

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Table 2. Parameter estimates exploring relationship between Final SPQ, Final BAT, SCR measures (at final exposure) and interoceptive accuracy for each cardiac timing group.

<b>SPQ</b>	<b>B</b>	<b>se</b>	<b>Beta</b>	<b>t</b>	<b>Sig</b>
Random	-6.351	3.802	-0.467	-1.671	0.126
Diastolic	-0.598	5.790	-0.024	-0.103	0.919
Systolic	25.799	6.872	0.653	3.754	0.001
<b>BAT</b>					
Random	5.504	2.563	0.562	2.148	0.057
Diastolic	-3.256	2.670	-0.276	-1.219	0.238
Systolic	-2.877	2.460	-0.265	-1.196	0.246
<b>SCR_Det</b>					
Random	17.721	12.536	0.398	1.370	0.200
Diastolic	-1.177	6.341	0.020	-0.196	0.855
Systolic	32.147	8.393	0.660	3.830	0.001
<b>SCR_Amp(Th)</b>					
Random	0.048	0.032	0.426	1.488	0.168
Diastolic	-0.004	0.014	-0.007	-0.254	0.802
Systolic	0.073	0.026	0.541	2.806	0.011
<b>SCR_Amp(UnTh)</b>					
Random	0.035	0.029	0.360	1.218	0.251
Diastolic	-0.006	0.024	-0.062	-0.268	0.792
Systolic	0.095	0.034	0.545	2.833	0.011

Key: SPQ – Spider Phobia Questionnaire; BAT – Behavioural Approach Task; SCR – Phasic Skin Conductance Response (Detected Events and Thresholded and Unthresholded Amplitudes). Significant results are highlighted.

## FIGURE LEGENDS

**Figure 1.** Each exposure session consisted of four presentation blocks separated by a short rest period. In each set participants saw 40 images, 35 spiders and 5 abstract shapes. Over the four exposures all subjects viewed the same spiders the same number of times. Anxiety levels were monitored intermittently throughout each session using a simple visual analogue scale (VAS). Psychological and behavioural assessments were performed before and after each exposure treatment.

**Figure 2.** Calculated adjusted mean SPQ scores for the three timing groups at the 25th, 50th and 75th percentile points for beat counting accuracy (equivalent to poor, moderate and good interoceptive performance). Benefits of systolic presentation can be seen to diminish compared to the other groups as interoception ability increases. See text for statistical detail.

**Figure 3.** Calculated adjusted mean behavioural avoidance task (BAT) scores (Stage Reached) for the three timing groups at the 25th, 50th and 75th percentile points for beat counting accuracy (equivalent to poor, moderate and good interoception ability). Both diastolic and systolic presentation showed an advantage in comparison with random presentation for individuals with poorer interoceptive skills, but this advantage diminished as these skills improved. See text for statistical detail.

**Figure 4.** Calculated adjusted mean phasic skin conductance response (SCR) amplitude values (thresholded) averaged across the final exposure session for the three cardiac timing groups at the 25th, 50th and 75th percentile points for beat counting accuracy (equivalent to poor, moderate and good performance). Higher interoceptive ability was associated with higher physiological reactivity at end of exposure intervention. Similar patterns were obtained for number of detected SCR events and unthresholded amplitude data.